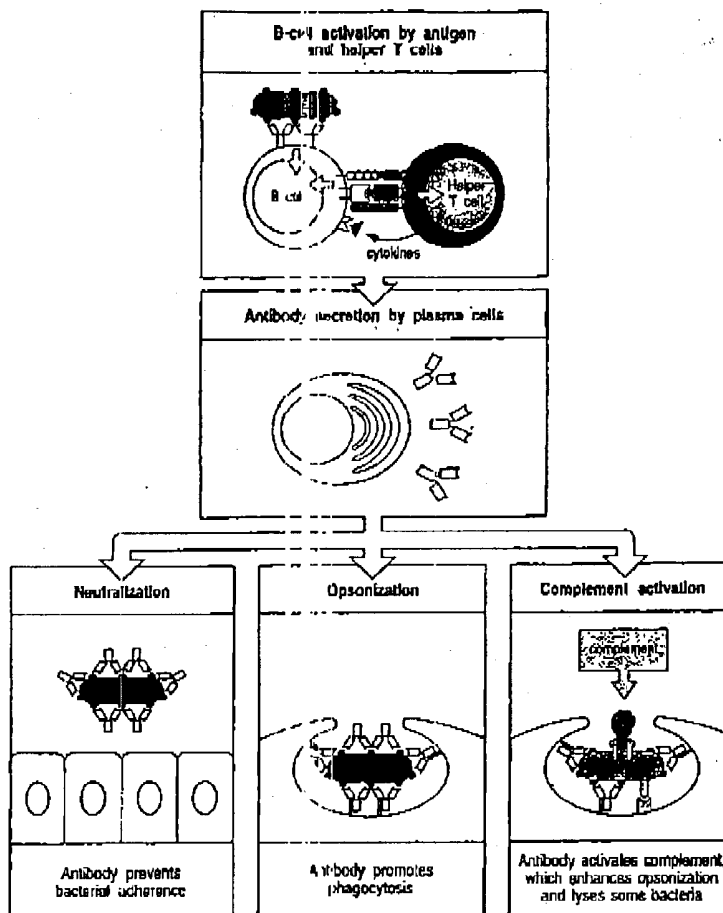


## EXHIBIT A

**Fig. 9.1 The humoral immune response is mediated by antibody molecules that are secreted by plasma cells.** Antigen that binds to the B-cell antigen receptor signals B cells and is, at the same time, internalized and processed into peptides that activate armed helper T cells. Signals from the bound antigen and from the helper T cell induce the B cell to proliferate and differentiate into a plasma cell secreting specific antibody (top two panels). There are three main ways in which these antibodies protect the host from infection (bottom panels). They can inhibit the toxic effects or infectivity of pathogens by binding to them; this is termed neutralization (left panel). By coating the pathogens, they can enable accessory cells that recognize their Fc portions of arrays of antibodies to ingest and kill the pathogen, a process called opsonization (middle panel). Antibodies can also trigger the complement cascade of proteins, which strongly enhance opsonization, and can directly kill some bacterial cells (right panel).



infection, and the terminal components of complement can lyse certain microorganisms directly by forming pores in their membranes. Which effector mechanisms are recruited in a particular response is determined by the isotypes of the antibodies produced.

The activation of B cells and their differentiation into antibody-secreting cells is triggered by antigen and usually requires helper T cells. The term 'helper T cell' is often used to mean a cell from the  $T_H2$  class of CD4 T cells, but a subset of  $T_H1$  cells can also help in B-cell activation. In this chapter we shall therefore use the term 'helper T cell' to mean any armed effector CD4 T cell that can activate a B cell. Helper T cells also control isotype switching and have a role in initiating somatic hypermutation of antibody variable (V)-region genes and directing the affinity maturation of antibodies that occurs during the course of a humoral immune response. In the first part of this chapter we shall describe the interactions of B cells with helper T cells and the mechanism of affinity maturation in the specialized microenvironment of peripheral lymphoid tissues. In the rest of the chapter we shall discuss in detail the mechanisms whereby antibodies contain and eliminate infections.